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COATINGS FOR IMPLANTABLE DEVICES INCLUDING BIOLOGICALLY ERODABLE POLYESTERS AND METHODS FOR FABRICATING THE SAME

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BACKGROUND

1. Field of the Invention

This invention is directed to coatings for drug delivery devices, such as drug eluting vascular stents, and methods for producing the same.

2. Description of the State of the Art

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially compress against the atherosclerotic plaque of the lesion to remodel the lumen wall. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

A problem associated with the above procedure includes formation of intimal flaps or torn arterial linings which can collapse and occlude the conduit after the balloon is deflated.

Moreover, thrombosis and restenosis of the artery may develop over several months after the procedure, which may require another angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis, a stent is implanted in the lumen to maintain the vascular patency.

Stents are used not only as a mechanical intervention but also as a vehicle for providing biological therapy. As a mechanical intervention, stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically, stents are capable of being compressed, so that they can be inserted through small vessels via catheters, and then expanded to a larger diameter once they are at the desired location. Examples in patent literature disclosing stents which have been applied in PTCA procedures include stents illustrated in U.S. Patent No. 4,733,665 issued to Palmaz, U.S. Patent No. 4,800,882 issued to Gianturco, and U.S. Patent No. 4,886,062 issued to Wiktor.

Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results. One proposed method for medicating stents involves the use of a polymeric carrier coated onto the surface of a stent. A solution which includes a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent. The solvent is allowed to evaporate, leaving on

the stent surface a coating of the polymer and the therapeutic substance impregnated in the polymer.

Among the polymers that have been proposed to be used in stent coatings are biologically absorbable and/or biologically erodable polymers. It is expected that using biologically absorbable and/or biologically erodable polymers may eliminate or at least reduce a chronic adverse in vivo response that is sometimes present when non-absorbable and/or non-erodable polymers are used. However, the drug release properties of some biologically absorbable and/or biologically erodable polymers may be insufficient for some drugs. In other words, the drug may be released from the polymer too quickly. Accordingly, there is a great need for biologically absorbable and/or biologically erodable polymers that allow for the drug to reside at the treatment site for an effective duration of time.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGs. 1 and 2 are microphotographs each showing a portion of a stent coated with a coatings according to embodiments of the present invention after the stimulated use test, as described by Examples.

FIG. 3 is a chart showing a profile of release of a drug from a stent coating fabricated according to an embodiment of the present invention.

FIGs. 4-7 are microphotographs each showing a portion of a stent coated with a coatings according to embodiments of the present invention after the wet expansion test, as described by Examples.

SUMMARY

A medical article comprising an implantable substrate having a coating is provided, the coating includes a first biologically erodable polymer having the glass transition temperature below about –50°C. The first polymer can include poly(esters), for example, poly(caprolactone), poly(4-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-hydroxybutyrate-co-3-hydroxyvalerate), and mixtures thereof. The coating can additionally include a biologically erodable polymeric additive mixed with the first polymer. According to one embodiment of the invention, the additive can be a polymer having the glass transition temperature of about –50°C or greater. According to another embodiment of the invention, the additive can be a polymer having a degree of crystallinity greater than that of the first polymer. Examples of additives that can be used include poly(3-hydroxybutyrate), poly(L-lactide), poly(D,L-lactide), poly(L-lactide-co-D,L-lactide), poly(glycolide), poly(glycolide-co-L-lactide), poly(glycolide-co-D,L-lactide), poly(caprolactone-co-L-lactide), poly(caprolactone-co-D,L-lactide), poly(trimethylene carbonate), copolymers of trimethylenecarbonate, poly(orthoesters), tyrosine derived poly(carbonates), poly(iminocarbonates), poly(ester-amides), and mixtures thereof. According to one embodiment of the invention, the mass ratio between the first polymer and the additive can be between about 9:1 and about 0.16:1.

A method for fabricating a medical article is provided, the method includes depositing a coating on at least a portion of an implantable substrate, the coating including a first biologically erodable polymer having the glass transition temperature below about –50°C.

DETAILED DESCRIPTION

1. Terms and Definitions

The following definitions apply in the present invention:

The term “biologically erodable” refers to coatings and/or polymers that are capable of being eroded, dissolved and/or degraded when exposed to bodily fluids such as blood and are gradually resorbed, absorbed and/or eliminated by the body. The processes of breaking down and eventual absorption and elimination of the coating and/or polymer can be caused by, for example, hydrolysis, metabolic processes, bulk or surface erosion, and the like.

Whenever the reference is made to “biologically erodable” stent coatings and/or polymers forming such stent coatings, it is understood that after the process of degradation, erosion, absorption, and/or resorption has been completed, no biologically erodable polymer will remain on the stent. In some cases, a very insignificant trace or residue of the biologically erodable polymer may, however, remain on the stent. Whenever the term “biologically erodable” is used in this application, it is intended to broadly include biologically erodable, biologically dissolvable, biologically degradable, biologically absorbable, and biologically resorbable coatings and/or polymers.

The “glass transition temperature” (T_g) is defined as a temperature approximately in the middle of the temperature region where the onset of segmental motion in the chains of the polymer occurs leading to the eventual transition of the polymer from a glassy solid to an amorphous solid at atmospheric pressure. To restate in other words, T_g is defined as an average temperature in the temperature region at which an amorphous polymer (or the

amorphous regions in a partially crystalline polymer) changes from a hard and relatively brittle condition to a viscoelastic (rubbery) condition. In some embodiments, T_g is intended to be the "average temperature" ±15°C, more narrowly, ±10°C. In some embodiments, T_g falls within the "average temperature" ±5°C.

The "melting temperature" (T_m) of a polymer is defined as the temperature at which the last trace of crystallinity in a polymer disappears as a sample is exposed to increasing heat. The T_m is always greater than the T_g for a given polymer.

For the purposes of the present invention, the T_g and T_m for all polymers discussed below have been determined using the method of differential scanning calorimetry (DSC). DSC measures the change in heat capacity of a polymer as the polymer is exposed to an increasing temperature. When T_g and T_m of a polymer or a blend of polymers is measured using DSC, in some embodiments T_g and/or T_m are designed to fall within about ±15°C of the measured temperature, more narrowly, within about ±10°C of the measured temperature. In some embodiments T_g and/or T_m are designed to fall within about ±5°C of the temperature measured by DSC.

The term or "degree of crystallinity" is defined as the fractional amount of crystalline phase in the polymer sample (by mass), assuming the sample can be subdivided into a crystalline phase and an amorphous phase. The phase is "crystalline" when a three-dimensional order on the level of atomic dimensions is present in the phase. The range of the three-dimensional order is below 50 nm in at least one direction. The degree of crystallinity can be determined by one or more of several experimental techniques, such as X-ray diffraction, calorimetry, density measurements, or infrared spectroscopy.

2. Embodiments of the Invention

A coating for an implantable medical device, such as a stent, according to embodiments of the present invention, can include any one or all of the following three layers:

(a) a primer layer;

(b) a drug-polymer layer (also referred to as "reservoir" or "reservoir layer") or alternatively a polymer free drug layer; and/or

(c) a topcoat layer.

Each layer of the stent coating can be formed on the stent by dissolving the polymer or a blend of polymers in a solvent, or a mixture of solvents, and applying the resulting polymer solution on the stent by spraying or immersing the stent in the solution. After the solution has been applied onto the stent, the coating is dried by allowing the solvent to evaporate. The process of drying can be accelerated if the drying is conducted at an elevated temperature.

To incorporate a drug into the reservoir layer, the drug can be combined with the polymer solution that is applied onto the stent as described above. Alternatively, to fabricate a polymer free drug layer, the drug can be dissolved in a suitable solvent or mixture of solvents, and the resulting drug solution can be applied on the stent by spraying or immersing the stent in the drug solution.

Instead of introducing the drug as a solution, the drug can be introduced as a colloidal system, such as a suspension in an appropriate solvent phase. To make the suspension, the drug can be dispersed in the solvent phase using conventional techniques used in colloid chemistry. Depending on a variety of factors, e.g., the nature of the drug, those having

ordinary skill in the art can select the solvent to form the solvent phase of the suspension, as well as the quantity of the drug to be dispersed in the solvent phase. The suspension can be mixed with a polymer solution and the mixture can be applied on the stent as described above. Alternatively, the drug suspension can be applied on the stent without being mixed with the polymer solution.

The drug-polymer layer can be applied directly onto at least a part of the stent surface to serve as a reservoir for at least one active agent or a drug which is incorporated into the reservoir layer. The optional primer layer or polymer-free drug layer can be applied between the stent and the reservoir to improve the adhesion of the drug-polymer layer to the stent. The topcoat layer can be applied over at least a portion of the reservoir layer and serves as a rate limiting membrane which helps to control the rate of release of the drug. The topcoat layer can be essentially free from any active agents or drugs.

The process of the release of the drug from a coating having a topcoat layer includes at least two steps. First, the drug can diffuse into the polymer of the topcoat layer at the drug-polymer layer/topcoat layer interface. A change in concentration of drug across this interface can result from differences in drug solubility between the two layers. Next, the drug can diffuse through the topcoat layer via the free volume between the macromolecules of the topcoat layer polymer. Next, the drug can arrive at the outer surface of the topcoat layer, and desorb from the outer surface. At this point, the drug is released into the blood stream or tissue. Consequently, the topcoat layer can serve as a rate limiting barrier.

According to embodiments of the present invention, any of the aforementioned layers or regions in a coating can be made from a biologically erodable polymer. In some

embodiments, the polymer is a polymeric blend. The polymeric blend comprises at least two polymers, each of which is a biologically erodable polymer. The composition of the blend in any of the layers can be the same or different. In some embodiments, only one of the layers can be made from a biologically erodable polymer or a blend, while the other layers can be made from other types of polymers. For example, the topcoat layer can be made from a biologically erodable polymer or a blend and the reservoir layer can be made from a conventional polymeric material or other sited materials.

The biologically erodable polymeric blend includes at least a principal polymer and a polymeric additive. In some embodiments, a bioabsorbable polyester having the glass transition temperature T_g below about –50°C can be used as the principal polymer. Examples of the principal polymers that can be used include poly(caprolactone) (PCL), poly(4-hydroxybutyrate), poly(3-hydroxyvalerate), grades of poly(3-hydroxybutyrate-co-3-hydroxyvalerate) having T_g below about –50°C, and mixtures thereof. In some embodiments, the coating can be free from one particular principal polymer. For example, the coating can be free from PCL.

The polymeric additive in the biologically erodable polymeric blend is added to reduce the rate of release of a drug from a stent coating. The polymeric additive that can be used can have (a) either T_g of about–50°C or greater, or (b) a degree of crystallinity greater than that of the principal polymer, or both (a) and (b). In some embodiments, T_g of the additive can be between about –50°C and about 80°C, more narrowly, between about –20°C and about 40°C, such as between about 0°C and about 20°C.

An example of a polymeric additive that can be used is poly(3-hydroxybutyrate) having the formula –[O–CH(CH_3)–CH_2–C(O)–O]$_n$– (3-PHB). T_g of 3-PHB is about 10°C, and T_m is about 179°C. Molecular weight of 3-PHB can be within a range of between about 100,000 and about 500,000 Daltons. 3-PHB can be obtained from Aldrich Chemical Company of Milwaukee, Wisconsin, or Goodfellow Corporation of Lancaster, Pennsylvania. Examples of other additives include poly(L-lactide), poly(D,L-lactide), poly(L-lactide-co-D,L-lactide), poly(glycolide), poly(glycolide-co-L-lactide), poly(glycolide-co-D,L-lactide), grades of poly(caprolactone-co-L-lactide) having T_g of about –50°C or higher, grades of poly(caprolactone-co-D,L-lactide) having T_g of about –50°C or higher, poly(trimethylene carbonate), copolymers of trimethylenecarbonate having T_g of about –50°C or higher, poly(orthoesters), tyrosine derived poly(carbonates), poly(iminocarbonates), poly(ester-amides), and mixtures thereof. In some embodiments, the coating can be free from any one of these additives.

The mass ratio between the principal polymer and the polymeric additive in the biologically erodable polymeric blend can be between about 9:1 and about 0.16:1, more narrowly, between about 6:1 and about 0.25:1, for example, between about 3:1 and about 0.33:1. One embodiment of the blend that can be used includes about 75 mass % PCL and the balance, 3-PHB. T_g of such blend can be raised to about –47°C, compared to about –62°C for pure PCL. The crystalline phases of the PCL and 3-PHB can both be present and retain distinct melting points. As a result, the elasticity of the polymeric material based on the blend can be lower than that of the pure PCL material depending on the degree of crystallinity of the samples.

As the crystallinity of 3-PHB is about 80% while that of PCL is about 57%, the crystallinity of the blend can be higher than that of the pure PCL material. Consequently, the reduction in rate of release of a drug from the stent coating can be anticipated for a stent coated with a PCL/3-PHB blend compared to a stent coated with pure PCL material based on the elevation of T_g and potential increase in degree of crystallinity.

Any layer of the stent coating can contain any amount of the biologically erodable polymeric blend described above. If less than 100% of the layer is made of the biologically erodable polymeric blend, other, alternative, polymers can comprise the balance. While it is preferred that the alternative polymers be biodegradable, they may also be permanent or non-biodegradable. Examples of the alternative polymers that can be used include polyacrylates, such as poly(butyl methacrylate), poly(ethyl methacrylate), and poly(ethyl methacrylate-co-butyl methacrylate), and fluorinated polymers and/or copolymers, such as poly(vinylidene fluoride) and poly(vinylidene fluoride-co-hexafluoro propene), poly(N-vinyl pyrrolidone), polydioxanone, polyorthoester, polyanhydride, polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, co-poly(ether-esters), polyalkylene oxalates, polyphosphazenes, biomolecules (such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid), polyurethanes, silicones, polyesters, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, vinyl halide polymers and copolymers (such as polyvinyl chloride), polyvinyl ethers (such as polyvinyl methyl ether), polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics (such as polystyrene), polyvinyl esters (such as polyvinyl acetate), copolymers of vinyl monomers with each other and olefins, e.g., poly(ethylene-co-vinyl alcohol) (EVAL), ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers;

polyamides (such as Nylon 66 and polycaprolactam), alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, and carboxymethyl cellulose.

Representative examples of some solvents suitable for making the stent coatings include N,N-dimethylacetamide (DMAC), N,N-dimethylformamide (DMF), tethrahydrofurane (THF), cyclohexanone, xylene, toluene, acetone, *i*-propanol, methyl ethyl ketone, propylene glycol monomethyl ether, methyl butyl ketone, ethyl acetate, *n*-butyl acetate, and dioxane. Some solvent mixtures can be used as well. Representative examples of the mixtures include:

(1) DMAC and methanol (e.g., a 50:50 by mass mixture);

(2) water, *i*-propanol, and DMAC (e.g., a 10:3:87 by mass mixture);

(3) *i*-propanol, and DMAC (e.g., 80:20, 50:50, or 20:80 by mass mixtures);

(4) acetone and cyclohexanone (e.g., 80:20, 50:50, or 20:80 by mass mixtures);

(5) acetone and xylene (e.g. a 50:50 by mass mixture);

(6) acetone, FLUX REMOVER AMS, and xylene (e.g., a 10:50:40 by mass mixture); and

(7) 1,1,2-trichloroethane and chloroform (e.g., a 80:20 by mass mixture).

FLUX REMOVER AMS is trade name of a solvent manufactured by Tech Spray, Inc. of Amarillo, Texas comprising about 93.7% of a mixture of 3,3-dichloro-1,1,1,2,2-pentafluoropropane and 1,3-dichloro-1,1,2,2,3-pentafluoropropane, and the balance of methanol, with trace amounts of nitromethane. Those having ordinary skill in the art will select the solvent or a mixture of solvents suitable for a particular polymer being dissolved.

The therapeutic substance can include any substance capable of exerting a therapeutic or prophylactic effect for a patient. The therapeutic substance may include small molecule substances, peptides, proteins, oligonucleotides, and the like. The therapeutic substance could be designed, for example, to inhibit the activity of vascular smooth muscle cells. It can be directed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells to inhibit restenosis.

Examples of therapeutic substances that can be used include antiproliferative substances such as actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich of Milwaukee, Wisconsin, or COSMEGEN available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I_1, actinomycin X_1, and actinomycin C_1. The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g. TAXOL® by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g. Taxotere®, from Aventis S.A., Frankfurt, Germany), methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin® from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g. Mutamycin® from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of antiplatelets,

anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as ANGIOMAX (Biogen, Inc., Cambridge, Mass.). Examples of cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g. Capoten® and Capozide® from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g. Prinivil® and Prinzide® from Merck & Co., Inc., Whitehouse Station, NJ), calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor® from Merck & Co., Inc., Whitehouse Station, NJ), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, tacrolimus, dexamethasone, and rapamycin and structural derivatives or functional analogs thereof, such as 40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of EVEROLIMUS available from Novartis), 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-O-tetrazole-rapamycin.

The coatings and methods of the present invention have been described with reference to a stent, such as a balloon expandable or self-expandable stent. The use of the coating is not limited to stents, however, and the coating can also be used with a variety of other medical devices. Examples of the medical device, that can be used in conjunction with the embodiments of this invention include stent-grafts, grafts (e.g., aortic grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, axius coronary shunts and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt-chromium alloys (e.g., ELGILOY), stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, tantalum-based alloys, nickel-titanium alloy, platinum, platinum-based alloys such as, e.g., platinum-iridium alloy, iridium, gold, magnesium, titanium, titanium-based alloys, zirconium-based alloys, or combinations thereof. Devices made from bioabsorbable or biostable polymers can also be used with the embodiments of the present invention.

"MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co. of Jenkintown, Pennsylvania. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum.

3. Examples

The following examples are provided to further illustrate embodiments of the present invention.

Example 1

A first composition was prepared by mixing the following components:

(a) about 2.0 mass % poly(caprolactone) (PCL); and

(b) the balance, a solvent blend, the blend comprising tetrahydrofuran (THF) and xylene in a mass ratio between THF and xylene of about 3:1.

The first composition was sprayed onto the surface of a bare 12 mm VISION stent (available from Guidant Corporation) and dried to form a stent coating. A spray coater was used having a 0.014 fan nozzle maintained at about 60°C with a feed pressure of about 0.2 atm (about 3 psi) and an atomization pressure of about 1.3 atm (about 20 psi). The dry stent coating contained about 300 μg of PCL. To remove the solvent, the coating was baked at about 60°C for about 2 hours.

The PCL coated stent was then subjected to a simulated use test. To test, an assembly comprising the PCL coated stent and a delivery catheter was made by crimping the stent on the catheter. The assembly was guided through a tortuous path and then deployed in a poly(vinyl alcohol) lesion having approximate size of about 3 by 10 millimeters. The tortuous path and the lesion contained de-ionized water at about 37°C. To deploy the stent, pressure of about 16 atm was applied to the balloon for about 1 minute, followed by deflating of the balloon and retraction of the catheter. After the catheter was retracted, de-ionized water was pumped through the tortuous path and the lesion for about 1 hour at a rate of about 50 milliliters per minute. Water was maintained at about 37°C. After 1 hour, the stent was removed from the poly(vinyl alcohol) lesion, dried, and prepared for analysis by scanning electron microscopy. An overall view of the stent after the simulated use test is shown by

FIG. 1. As can be seen, the stent coating showed good mechanical integrity and the coating was uniform and smooth.

Example 2

A first composition was prepared by mixing the following components:

(a) about 2.0 mass % PCL; and

(b) the balance, a solvent blend, the blend comprising THF and xylene in a mass ratio between THF and xylene of about 3:1.

The first composition was sprayed onto the surface of a bare 12 mm VISION stent, dried and baked as described in Example 1 to form a dry primer layer. The dry primer layer contained about 100 μg of PCL.

A second composition was prepared by mixing the following components:

(a) about 2.0 mass % EVEROLIMUS; and

(b) the balance, a solvent blend, the blend comprising acetone and xylene in a mass ratio between acetone and xylene of about 3:2.

The second composition contained about 200 μg EVEROLIMUS. The second composition was applied onto the dried primer layer to form the reservoir layer.

A third composition was prepared by mixing the following components:

(a) about 2.0 mass % PCL; and

(b) the balance, a solvent blend, the blend comprising THF and xylene in a mass ratio between THF and xylene of about 3:1.

The third composition was sprayed onto the dry reservoir layer, dried and baked as described in Example 1, to form a dry topcoat layer. The dry topcoat layer contained about 400 µg of PCL.

The coated stent was then subjected to a simulated use test described above. An overall view of the stent after the simulated use test is shown by FIG. 2. As can be seen, the stent coating showed good mechanical integrity and the coating was uniform and smooth.

Example 3

The stent coating made as described in Example 2 was also tested for drug release. The stent was immersed in an aqueous solution containing about 1 mass % TRITON X-100 surfactant. TRITON is trade name of a condensate of *p*-octylphenol with ethylene oxide registered to Rohm & Haas Co. and available from Aldrich Co. The solution was maintained at a temperature of about 37°C, and the drug release was measured by assaying the solution using the high pressure liquid chromatography (HPLC) method after 1, 3, 6, and 9 hours, while the temperature of the solution was maintained constant at about 37°C. As shown by the graph presented by FIG. 3, essentially the entire amount of EVEROLIMUS was released within 6 hours.

Example 4

A first composition was prepared by mixing the following components:

(a) about 2.0 mass % poly(3-hydroxybutyrate) (3-PHB); and

(b) the balance, a solvent blend, the blend comprising 1,1,2-trichloroethane (TCE) and chloroform in a mass ratio between TCE and chloroform of about 4:1.

The first composition was sprayed onto the surface of a bare 12 mm VISION stent, dried and baked as described in Example 1 to form a stent coating.

The stent coated with 3-PHB was then subjected to a wet expansion test. To test, an assembly comprising the coated stent and a delivery catheter was made by crimping the stent on the catheter, followed by immersion in de-ionized water, which was maintained at about 37°C. The stent was expanded while wet, followed by deflating the catheter, removing and drying the stent. An overall view of the stent after the wet expansion test is shown by FIG. 4. As can be seen, the stent coating has developed cracks at the high strain joints.

Example 5

A primer and reservoir layers were formed on a 12 mm VISION stent as described in Example 2. A composition was then prepared by mixing the following components:

(a) about 0.75 mass % PCL;

(b) about 0.25 mass % 3-PHB; and

(c) the balance, a solvent blend, the blend comprising TCE and chloroform in a mass ratio between TCE and chloroform of about 4:1.

The composition was sprayed onto the dry reservoir layer, dried and baked, to form a dry topcoat layer. The dry topcoat layer contained about 400 μg of the PCL/3-PHB mixture.

The coated stent was then subjected to a wet expansion test described in Example 4.

An overall view of the stent after the wet expansion test is shown by FIG. 5. As can be seen, the stent coating showed good mechanical integrity. The coating was uniform and smooth.

Example 6

A primer and reservoir layers were formed on a 12 mm VISION stent as described in Example 2. A composition was then prepared by mixing the following components:

(a) about 0.5 mass % PCL;

(b) about 0.5 mass % 3-PHB; and

(c) the balance, a solvent blend, the blend comprising TCE and chloroform in a mass ratio between TCE and chloroform of about 4:1.

The composition was sprayed onto the dry reservoir layer, dried and baked as described in Example 1, to form a dry topcoat layer. The dry topcoat layer contained about 400 μg of the PCL/3-PHB mixture.

The coated stent was then subjected to a wet expansion test described in Example 4. An overall view of the stent after the wet expansion test is shown by FIG. 6. As can be seen, the stent coating showed good mechanical integrity and the coating was uniform and smooth.

Example 7

A primer and reservoir layers were formed on a 12 mm VISION stent as described in Example 2. A composition was then prepared by mixing the following components:

(a) about 0.25 mass % PCL;

(b) about 0.75 mass % 3-PHB; and

(c) the balance, a solvent blend, the blend comprising TCE and chloroform in a mass ratio between TCE and chloroform of about 4:1.

The composition was sprayed onto the dry reservoir layer, dried and baked, to form a dry topcoat layer. The dry topcoat layer contained about 400 µg of the PCL/3-PHB mixture.

The coated stent was then subjected to a wet expansion test described in Example 4. An overall view of the stent after the wet expansion test is shown by FIG. 7. As can be seen, the stent coating showed good mechanical integrity. The coating was uniform and smooth.

Example 8

The stents were additionally assayed for drug release. The stents were immersed in stirred porcine serum at about 37°C for about 24 hours to simulate an *in vivo* environment. The stents coated according to Examples 2, 4, 5, and 6 were used. The amount of the drug remaining on the stent was measured using HPLC. The results are summarized in Table 1.

Table 1. Drug Release in Porcine Serum

No.	Stent Of Example No.	Primer	Reservoir	Topcoat	EVEROLIMUS Released After 24 Hours in Porcine Serum, %
1	2	PCL, 100 µg	EVEROLIMUS, 200 µg	PCL,400 µg	100
3	6	PCL, 100 µg	EVEROLIMUS, 200 µg	PCL/3-PHB, 400 µg (PCL/3-PHB ratio is 1:1)	72
4	7	PCL, 100 µg	EVEROLIMUS, 200 µg	PCL/3-PHB, 400 µg (PCL/3-PHB ratio is 1:3)	37

As seen from Table 1, after exposure to the porcine serum, the entire amount of EVEROLIMUS was released within 24 hours from the stent of Example 2, which had no 3-PHB in the topcoat. At the same time, the stent coated with a 3-PHB-containing coating released substantially smaller amount of the drug after 24 hour exposure.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.